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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,451	SCHOFIELD ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 79-137* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,9-16,18,81-88,100,102-106,108-110,116-120,124 and 125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 4-8,17,18,79,80,89-99,101,107,111-115,121-123 and 126-137.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/31/06 has been entered.

Applicant's amendment filed 8/31/06 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-18 and 79-125), and species election of inducing an immune response, upregulation of the Th2 response, treatment or prophylaxis of the disease condition malaria using a GPI with the sequence EtN-P-[Mα2]Mα2Mα6Mα4Gα6Ino-Y in Applicant's response filed 10/17/03.

Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of: (1) the claimed method of activating CD1-restricted Th (including CD1+ NK1.1+ T cells, Th2) cells comprising administration of a GPI derivative or equivalent thereof (claims 11-13, 86-88 and 116-118), or complex thereof (all instant claims), including for treatment or prophylaxis via administration of a GPI derivative or equivalent thereof or complex thereof.

The instant claims encompass use of a derivative or equivalent of GPI or a complex of GPI that comprises a molecule other than a protein or peptide antigen to activate or induce Th cells *in vitro* or *in vivo*, including treatment or prophylaxis.

The specification discloses that GPIs consist of a conserved core glycan (Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI (sentence spanning pages 1 and 2). The specification further discloses other GPI that do not appear to comprise the conserved core glycan as defined above (pages 3-7), for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) or Manα2-Manα6-M-Y (page 7 at line 1). The specification discloses that "derivatives" or "equivalents" should be understood to include reference to fragments, parts, portions, chemical equivalents, mutants, homologs and analogs, and further that equivalents may not necessarily be derived from GPI but may share certain conformational similarities, or alternatively, chemical equivalents may be specifically designed to mimic certain physiochemical properties of GPI and may also include synthetic carbohydrates and peptide mimetics (page 15 at lines 2-11). The specification further discloses that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page 20 at lines 29-31).

The specification as filed does not provide written description support for derivative or equivalent; the skilled artisan cannot envision all the contemplated substances by the label "derivative" or "equivalents" and therefore conception cannot be not achieved until reduction to practice has occurred. The specification as filed does not provide written description support for any molecule in complex with "a GPI moiety" except for an antigenic peptide or protein. Adequate written description requires more than a mere statement that it is part of the invention and along with a recitation of a function such as inducing Th cells. The derivative or equivalent itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the peptide has, and if one extends the analysis in the instant case, what the peptide does (*i.e.,* it induces a CD1-restricted Th cell response), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type

of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 8/31/06 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 16-17, briefly that: (1) Applicants has amended the independent claims to delete the reference to "derivative" or "equivalent" of GPI and to defined the structure of the GPI molecule by its conserved core glycan, (2) Applicant has amended the dependent claims to delete those formulas that do not contain the conserved core glycan, (3) the genus of GPI molecules encompassed by the present claims are now characterized both by a characteristic structural feature as well as a functional feature, *i.e.,* activating Th cells via an interaction and association with CD1.

It is the Examiner's position that: (1) Applicant has not amended the dependent claims 11, 86 and 116 to delete the reference to "derivative" or "equivalent" of GPI, (2) Applicant has not amended the dependent claims 11, 86 and 116 to delete all the formulae that do not contain the conserved core glycan, and (3) as such the structure of the GPI is not characterized.

5. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method of activating Th cells, inducing an immune response in a mammal directed to GPI, or treating malarial disease by administering GPI comprising the structure recited in the instant claims that binds to CD1 and activates NK1.1 CD4+ Th cells, or inducing an immune response in a mammal to a protein or peptide antigen linked to GPI, does not reasonably provide enablement for the claimed method of activating Th cells, inducing an immune response in a mammal directed to GPI, or to an antigen that is linked to GPI wherein said antigen is not a peptide or protein antigen and/or the GPI is a derivative or equivalent such as recited in the instant claim 97, or prophylaxis of malarial disease or of any other disease condition by administering a GPI derivative or equivalent or complex of any of these. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims encompass activating Th cells or inducing an immune response, including for treatment and/or prophylaxis, including prevention, of any mammalian disease condition with GPI "complexes" or GPI "derivatives" or "equivalents" of GPI that the specification does not disclose how to make and/or use, the GPI "derivatives" or "equivalents" that are not necessarily substitution variants of the defined structures recited in instant claims, the molecule in the GPI "complex" not necessarily a peptide or protein antigen, and prevention of any disease using any of GPI, GPI complexes, GPI equivalents or GPI derivatives.

The specification discloses that GPIs consist of a conserved core glycan (Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI (sentence spanning pages 1 and 2). The specification further discloses other GPI that do not appear to comprise the conserved core glycan as defined above (pages 3-7), for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) or Manα2-Manα6-M-Y (page 7 at line 1). The specification discloses that "derivatives" or "equivalents" should be understood to include reference to fragments, parts, portions, chemical equivalents, mutants, homologs and analogs, and further that equivalents may not necessarily be derived from GPI but may share certain conformational similarities, or alternatively, chemical equivalents may be specifically designed to mimic certain physiochemical properties of GPI and may also include synthetic carbohydrates and peptide mimetics (page 15 at lines 2-11). The specification further discloses that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page 20 at lines 29-31).

The disclosed use of the invention is to regulate the Th1/Th2 response in order to therapeutically or phrophylactically treat disease conditions that show a pronounced Th1/Th2 dependence such as cerebral malaria, tuberculosis, leprosy, leishmaniasis, type I diabetes, autoimmune arthritis, SLE and erythromatosis, cancer, or others, and/or providing B cell help for antibody production by inducing a Th2 response (especially paragraph spanning pages 35-36).

The specification does not disclose any working examples of treatment or prophylaxis of any condition or disease *in vivo*, including in a mammal, comprising administration of GPI, derivatives or equivalents, nor of prophylaxis of any disease using GPI.

Evidentiary reference Carvalho *et al* (Scand. J. Immunol. 2002, 56: 327-343) teach that an effective malaria vaccine is not yet available. Carvalho *et al* teach that an astonishing amount of data has accumulated concerning parasite biology, host-parasite interactions, immunity and escape mechanisms, targets and modulators of immune responses, but nevertheless, this knowledge has not been enough to make us understand how to properly manipulate the whole system to build an effective vaccine (especially abstract). Carvalho *et al* teach that the acquisition of immunity in malaria is still far from being a well-understood phenomenon, and that no reliable correlates of

protection have been identified so far, turning malaria vaccine research into an essentially empirical or semi-empirical approach (especially paragraph spanning pages 329-330). Carvalho *et al* teach that murine malaria is quite different from human malaria, and the mechanisms of immunity acting in such models may have no relevance for humans (especially paragraph spanning columns 1-2 on page 330). Carvalho *et al* teach "In conclusion, we would like to stress that most of the data supporting the current vaccine candidate antigens rely on the three above approaches, *i.e.,* epidemiological associations between protection and antigen recognition by exposed individuals, antiparasitic effect *in vitro* and experiments in animal models. As their relevance is far from being well established and consensual, they mostly function as a guide rather than as a secure way for finding and studying potential candidate antigens. It means that many times the bet on a new antigen is a shot in the dark." (especially first full paragraph, column 2 on page 330).

Evidentiary reference de Souza *et al* (Infect. Immun. 70(9): 5045-551, 2002) teach that "While GPIs may be involved in the pathogenesis of human malaria, the data from this study [*i.e.,* assessing levels of anti-GPI antibodies in plasma from persons living in areas of seasonal malaria transmission in the Gambia] do not provide any strong evidence to support the notion that anti-GPI antibodies confer resistance to mild or severe malarial disease." (especially abstract).

Evidentiary reference Websters Online Dictionary teaches that prophylaxis is the prevention of disease, and that prophylaxis refers to any medical or public health procedure whose purpose is to prevent, rather than treat or cure, disease.

Evidentiary reference MedicineNet.com teaches that prophylaxis is a measure taken for the prevention of a disease or condition.

Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 8/31/06 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 17-19, briefly, as regards the instant rejection that: (1) Applicant has canceled the recitation of "derivative" or "equivalent," (2) that the argument to treatment or prophylaxis should apply only, if at all, to claims 103, 109, 124 and their dependent claims.

It is the Examiner's position that: (1) Applicant has not amended the dependent claims 11, 86 and 116 to delete the reference to "derivative" or "equivalent," (2) that although the instant specification has disclosed "prophylaxis does not necessarily mean that the subject will not eventually contract a disease condition" (specification at page 45, first

sentence), the cited evidentiary references define prophylaxis as the prevention of a disease or condition, rather than the treatment of a disease or a condition.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 11-13, 86-88 and 116-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 86 and 116 recite the limitations "Mα2 [Mα2][G]Mα6Mα4Gα6Ino-Y," "Mα2[Mα2][X]Mα6Mα4Gα6Ino-Y," and "or derivatives or equivalents thereof." There is insufficient antecedent basis for these limitations in the claim. Base claims 1, 81 and 109 recite the limitation "wherein the GPI molecule comprises Mα2Mα6Mα4Gα6Ino-Y." The said limitations in claims 11, 86 and 116 do not comprise the formula recited in the said base claims as they contain an additional constituent in the middle of the formula, or they are derivatives or equivalents that do not necessarily comprise the formula recited in the said base claims.

8. For the purpose of prior art rejections, the filing date of the instant claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 is deemed to be the filing date of the PCT application PCT/AU99/00929, *i.e.,* 10/27/99, as the foreign priority application AU PP 6758 does not support the claimed limitations of the instant application. There is no disclosure of the chemical species recited in the said instant claims in the said foreign priority application.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 9-16, 18, 81-88, 100 and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record) as evidenced by Nagata *et al* (Eur. J. Immunol. 1993 23: 1193-1196, of record), Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143), Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606), Berhe *et al* (Mol. Biochem. Parasit. 1999 103: 273-278), Schofield *et al* (Science 283: 225-229, 1/8/99, of record), Joyce *et al* (Science 1998 279: 1541-1543, IDS reference) and Sieling *et al* (Science 1995 269: 227-230, IDS reference).

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).
Evidentiary reference Nagata *et al* teach that Th2 cells secrete IL-4, IL-5 and IL-6 and provide the major help for antibody production of T cells (especially first paragraph on page 1193).

Evidentiary reference Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the evidentiary reference Gerold *et al* (1994) cited below (see entire article).

Evidentiary reference Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article).

Evidentiary reference Berhe *et al* teach GPIs from different isolates of *Plasmodium falciparum,* including the isolate taught by the art reference Schofeld *et al* (1993), have a set of GPIs structurally identical to the GPIs described for the reference parasite line FCBR, and the core structure is ethanolamine-phosphate-Mα2Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol or ethanolamine-phosphate-Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol, and wherein the GPIs have ester linked fatty acids at the C-terminal end (see entire article).

Evidentiary reference Schofield *et al* (1999) teach that the GPI anchors in *Plasmodium falciparum* comprise the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4-GlcNα6-myoinositol phosphate-diacyl glycerol (see entire reference, especially Figure 1A). Schofield *et al* (1999) further teach that the proliferative and IL-4 (*i.e.,* Th2 cytokine) response to PfGPI of NK 1.1+/CD4+ T cells is independent of MHC and can be blocked by an anti-CD1 mAb, indicating CD1 restriction.

Evidentiary reference Joyce *et al* teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

Evidentiary reference Sieling *et al* teach GPI-CD1-mediated stimulation of T cell subsets, the GPI from mycobacterial species possessing a phosphatidylinositol aspect similar to the GPI taught by the other evidentiary references cited herein.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments in the amendment filed 8/31/06 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 19-20, briefly that: the Schofield *et al* reference teaches that GPI is a toxin of malaria parasites and acts as a T-independent antigen, eliciting responses from B-cells without T cell help, GPIs are a complex class of molecules and the present presently claimed methods are directed to administration of GPI characterized by a specified core glycan and capable of activating T cells via interaction with CD1, and the art reference does not teach the structure of GPI molecules that is required to induce a CD1 restricted response.

It is the Examiner's position that: (1) it is an inherent property of art method that administration of GPI results in GPI binding to CD1d and that the resulting complexes activate NK1.1 Th cells (and as evidenced by the Schofield *et al* evidentiary reference (1999) that teaches that IgG production was regulated through IL-4-producing CD4+ NK1.1 Th cells that recognize GPI/CD1d complexes), (2) the instant claims recite activation of Th cells by administering GPI, (3) the GPIs taught by the art reference have the core structure recited in the instant claims as evidenced by the cited evidentiary references, and (4) the instant rejection is not an obviousness-type rejection, but rather anticipation.

11. Claims 1-3, 9-16, 18, 81-88, 100 and 102 are rejected under 35 U.S.C. 102(a) as being anticipated by Schofield *et al* (Science 283: 225-229, 1/8/99) as evidenced by van Joost *et al* (J. Amer. Acad. Dermatol. 27: 922-8, 1992) and Paul (Fundamental Immunol. 2nd Ed., 1989, New York, Raven Press, page 405).

Schofield *et al* teach COOH-terminal GPIs from P. *falciparum* and T. *brucei* that have the same structure as the elected species, as well as GPIs from other sources such as parasitic protozoa (especially Figure 1 and page 228). Schofield *et al* further teach CD1-restricted recognition of GPI moieties, including those linked to diacylglycerol or alkylacylglycerol (especially paragraph 1, column 1 on page 227), by $CD4^+$ NK1.1 Th cells, and production of high levels of IL-4 (involved in Th2 type responses). Schofield *et al* teach activating Th cells and resulting IgG1 formation in MHC class II -/- mice by injecting PfGPI-linked to an antigen (purified P. *falciparum* GPI), the response proceeding from CD1d-restricted presentation of GPI to NK1.1+ CD4+ T cells (especially paragraph spanning pages 226-227 and paragraph spanning columns 1-2 on page 228).

Evidentiary reference van Joost *et al* teaches that Th2 lymphocytes produce IL-4 (especially page 922), and evidentiary reference Paul teaches that Th2 cells produce IL-4 and that IL-4 induces IgG1 and IgE production from B cells.

It is noted by the Examiner that Applicant has indicated in the amendment filed 8/31/06 on pages 20-21 that Applicant intends to submit a Katz Declaration to overcome the instant rejection; however, the Examiner may not withdraw the instant rejection.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the Gerold *et al* (1994) cited below. Gerold *et al* (1996) teach that antibodies to malarial GPIs are able to block cytokine induction by whole parasite extracts, that the said GPIs are the major toxin of malarial origin and that they play a central role in the etiology of clinical severe and cerebral malaria (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the malarial GPI taught by either Gerold *et al* reference as the GPI taught by WO 99/52547 in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

14. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Schofield *et al* (Science 283: 225-229, 1/8/99, of record).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including also inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Schofield *et al* teach COOH-terminal GPIs from P. *falciparum* and T. *brucei* that have the same structure as the elected species, as well as GPIs from other sources such as parasitic protozoa (especially Figure 1 and page 228). Schofield *et al* further teach CD1-restricted recognition of GPI moieties, including those linked to diacylglycerol or alkylacylglycerol (especially paragraph 1, column 1 on page 227 and paragraph spanning pages 227-228), by $CD4^+$ NK1.1 Th cells, and production of high levels of IL-4 (involved in Th2 type responses). Schofield *et al* teach activating Th cells and resulting IgG1 formation in MHC class II -/- mice by injecting PfGPI-linked to an antigen (*i.e.,* a purified P. *falciparum* GPI complex such as that recited in the instant claims), the response proceeding from CD1d-restricted presentation of GPI to NK1.1+ CD4+ T cells (especially paragraph spanning pages 226-227 and paragraph spanning columns 1-2 on page 228). Schofield *et al* teach that MHC restricted non-responsiveness to malarial surface antigens has been proposed to be a major obstacle to the development of vaccines, but because both human and murine CD1 molecules are relatively nonpolymorphic, GPI anchors may provide universal T cell sites, overcoming MHC restriction in antibody responses to various pathogens (especially last paragraph of article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and Schofield *et al* teach the structure of a P. *falciparum* GPI that is recognized by CD4+ NK1.1 T cells after being bound to CD1.

15. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

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WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/52547.

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16. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143).

WO 99/12562 A1 teaches treatment parasitic infections in a mammal, including malaria, comprising administering a CD1-restricted antigen such as a GPI that comprises a hydrophilic component conjugated to a hydrophobic component that comprises one or more saturated or unsaturated acyl chains and wherein one or more of the acyl chains is bonded to a phosphate group. WO 99/12562 A1 teaches that glycosyl phosphatidylinositols (GPIs) have two alkyl chains and a hydrophilic head group that conform to the CD1d motif and are presented by CD1d in both humans and mice (especially abstract, page 3 at lines 8-15, page 16 at lines 25-30, page 28 at lines 15-33, page 29 at lines1-10, claims 10-17).

WO 99/12562 A1 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/12562 A1 teaches treating malaria by administering CD1-binding GPI to induce a T cell response and treat malaria, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

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on page 228). Schofield *et al* teach that MHC restricted non-responsiveness to malarial surface antigens has been proposed to be a major obstacle to the development of vaccines, but because both human and murine CD1 molecules are relatively nonpolymorphic, GPI anchors may provide universal T cell sites, overcoming MHC restriction in antibody responses to various pathogens (especially last paragraph of article).

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18. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

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and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

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19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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